UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/852,965	05/10/2001	Scott F. Sneddon	2478.1002-002	4903

21005 7590 09/30/2003

HAMILTON, BROOK, SMITH & REYNOLDS, P.C.
530 VIRGINIA ROAD
P.O. BOX 9133
CONCORD, MA 01742-9133

EXAMINER
BALASUBRAMANIAN, VENKATARAMAN

ART UNIT	PAPER NUMBER
1624	

DATE MAILED: 09/30/2003

17

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/852,965	SNEDDON ET AL.	
	Examiner	Art Unit	
	Venkataraman Balasubramanian	1624	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *31 July 2003* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *15-32,71-100 and 109-160* is/are pending in the application.

4a) Of the above claim(s) *109-160* is/are withdrawn from consideration.

5)☐ Claim(s) *30-32* is/are allowed.

6)☐ Claim(s) *15,16,20-23,26,27,29 and 71-100* is/are rejected.

7)☐ Claim(s) *17-19,24,25 and 28* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Applicants' response, filed on 7/31/2003, is made of record.

Applicants' response, which included cancellation of claims 108, 138,154, is and amendment to claim 79, filed on 7/31/2003, is made of record.

Claims 15-32, 71-100 and 109-160 are now are pending. Of which claims 109-160 are with drawn from consideration for reasons of record in paper #12.

Claims 15-32 and 71-100 are under examination.

Applicants' traversal that examiner has not provided any reasons for withdrawing claims 109-160, is incorrect. To repeat:

Newly submitted claims 109-160 directed to an invention that is independent or distinct from the invention originally claimed for the following reasons: The compound and the method of use is distinct and independent as evident from the instant claims and would have been subjected to restriction requirement made in the paper # 6.

Since applicant has received an action on the merits for the originally presented invention, this invention has been constructively elected by original presentation for prosecution on the merits. Accordingly, claims 109-160 are withdrawn from consideration as being directed to a non-elected invention. See 37 CFR 1.142(b) and MPEP § 821.03.

In short if applicants had provided claims 109-160 originally, at the time of restriction examiner would have considered these claims and restricted accordingly.

Hence, withdrawal claims 109-160 is proper as per 37 CFR 1.142(b) and MPEP § 821.03.

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

Inventorship

Applicants' correction of inventorship to add John. M. Williams, and Hans-Peter-Biemann as two new inventors, is acknowledged. However, An oath or declaration by each actual inventor or inventors listing the entire inventive entity has not been submitted. As noted by the applicants, the signature of inventor Quio is needed.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 71-100 and 108 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for rheumatoid arthritis, does not reasonably provide enablement for any or all TNF-α mediated condition in a patient including those yet to be discovered as due to TNF-α. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims for reasons of record. To repeat:

The instant claims 71-100 and 108 are drawn to "treating TNF-α mediated condition ". The scope of the claims includes not only any or all conditions but also those condition yet to be discovered for which there is no enabling disclosure. In addition, the scope of these claims includes treatment of various diseases, which is not adequately enabled solely based on the inhibiting expression of TNF-α activity of the compounds provided in the specification pages 15-17. The instant compounds are disclosed to inhibit TNF-α activity and it is recited that the instant compounds are therefore useful in treating any or all diseases where TNF-α activity is implicated, for which applicants provide no competent evidence. Furthermore, the applicants have not provided any competent evidence that the instantly disclosed tests are highly predictive for all the uses disclosed and embraced by the claim language for the intended host. That a single class of compounds can be used to treat all diseases embraced in the claims is an incredible finding for which applicants have not provided supporting evidence. Moreover many if not most of diseases such as, multiple sclerosis, AIDS, malignant diseases etc. are very difficult to treat and at present there is no known drug, which can successfully reverse the course of these diseases, despite the fact that there are many drugs, which can be used for "inflammatory condition". Note substantiation of utility and its scope is required when utility is "speculative", "sufficiently unusual" or not provided. See Ex parte Jovanovics, 211 USPQ 907, 909; In re Langer 183 USPQ 288. Also note Hoffman v. Klaus 9 USPQ 2d 1657 and Ex parte Powers 220 USPQ 925 regarding type of testing needed to support in vivo uses. Next, applicant's attention is drawn to the Revised Interim Utility and Written Description Guidelines, at 64 FR 71427 and 71440 (December 21, 1999) wherein it is

emphasized that 'a claimed invention must have a specific and substantial utility'. The disclosure in the instant case is not sufficient to enable the instantly claimed method treating solely based on the inhibitory activity disclosed for the compounds. The state of the art is indicative of the requirement for undue experimentation. See Graninger et al. Curr. Opin. Rhematol. 13(3) 209-13, 2001 (PubMed Abstract provided) and Shaw et al. Expert Opin. Investig. Drugs 9(7) 1469-1478, 2000 (PubMed Abstract provided).

In evaluating the enablement question, several factors are to be considered. Note *In re Wands*, 8 USPQ2d 1400 and *Ex parte Forman*, 230 USPQ 546. The factors include: 1) The nature of the invention, 2) the state of the prior art, 3) the predictability or lack thereof in the art, 4) the amount of direction or guidance present, 5) the presence or absence of working examples, 6) the breadth of the claims, and 7) the quantity of experimentation needed.

1) The nature of the invention: Therapeutic use of the compounds in treating diseases that require inhibition of TNF-α activity.

2) The state of the prior art: A very recent publication expressed that treating disease by the inhibition of TNF-α is still exploratory. See references cited above.

3) The predictability or lack thereof in the art: Applicants have not provided any competent evidence or disclosed tests that are highly predictive for the pharmaceutical use for treating any or all condition of the instant compounds. Pharmacological activity in general is a very unpredictable area. Note that in cases involving physiological activity such as the instant case, "the scope of enablement obviously varies inversely

with the degree of unpredictability of the factors involved". See *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970).

4) The amount of direction or guidance present and 5) the presence or absence of working examples: Specification has no working examples to show treating any or all condition and the state of the art is that the effects of inhibiting TNF-α activity are unpredictable and at best limited to modulation of rheumatoid arthritis.

6) The breadth of the claims: The instant claims embrace any or all condition including those yet to be related to expression of TNF-α activity.

7) The quantity of experimentation needed would be an undue burden to one skilled in the pharmaceutical arts since there is inadequate guidance given to the skilled artisan, regarding the pharmaceutical use, for the reasons stated above.

Thus, factors such as "sufficient working examples", "the level of skill in the art" and "predictability", etc. have been demonstrated to be sufficiently lacking in the instant case for the instant method claims. In view of the breadth of the claims, the chemical nature of the invention, the unpredictability of receptor-ligand interactions in general, and the lack of working examples regarding the activity of the claimed compounds towards treating the variety of diseases of the instant claims, one having ordinary skill in the art would have to undergo an undue amount of experimentation to use the instantly claimed invention commensurate in scope with the claims.

This rejection is same as made in the previous office action. Applicants' argument to overcome this rejection is not persuasive.

1. Applicants' argument that examiner has not provided no rationale to question enablement of the claimed subject matter (point A of response) is totally incorrect. As can be seen from the above rejection, examiner states "See Graninger et al. Curr. Opin. Rhematol. 13(3) 209-13, 2001 (PubMed Abstract provided) and Shaw et al. Expert Opin. Investig. Drugs 9(7) 1469-1478, 2000 (PubMed Abstract provided)". Examiner has clearly provided support for the rejection citing two references and these references are included in the PTO 892.

2. As for point B, applicants' argument is misplaced. It is not whether the compound has a utility or not is the issue here. Whether the plethora compounds claimed would be useful in treating all or any diseases where TNF-α is implicated. Examiner has clearly provided evidence that prior art teaches use for rheumatoid arthritis not for any or all diseases embraced in the claim language. Thus Cross vs Iizuka cited by the applicants is not to the point.

3. Applicants' reliance on In re Brana is not proper. Brana is not to the point for the instant case. First of all the issue is not lack of FDA approval but whether the instant claims meet the 112 first paragraph requirement of the patent law. More specifically, as per Revised Interim Utility and Written Description Guidelines, at 64 FR 71427 and 71440 (December 21, 1999) 'a claimed invention must have a specific and substantial utility'. The disclosure in the instant case is not sufficient to enable the instantly claimed method treating solely based on the inhibitory activity disclosed for the compounds. Again note substantiation of utility and its scope is required when utility is "speculative", "sufficiently unusual" or not provided. See Ex parte Jovanovics, 211 USPQ 907, 909; In

re Langer 183 USPQ 288. Also note Hoffman v. Klaus 9 USPQ 2d 1657 and Ex parte Powers 220 USPQ 925 regarding type of testing needed to support in vivo uses.

In addition, applicants should note that the issue addressed in Brana is treating cancer in general is to be deemed as enablement of as class for all cancers. The diseases embraced in the instant claim language include any or all diseases and are therefore totally diverse. There is no evidence in the prior art that all these diseases are equivalent.

4. As for point C, none of the references cited by the applicants provide support for any or all diseases. In fact, careful analysis of the references, which are all, published in arthritis related journals, lend support to rheumatoid arthritis but not all or any diseases. In addition, applicants are arguing in one hand FDA approval is not a prerequisite but are providing FDA approval as support. Also the fact that monoclonal antibody is useful to treat Crohn's does not provide nexus for treating any or all diseases.

Hence this rejection is proper and is maintained.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 15-16, 20-23, 26-27 and 29 are rejected under 35 U.S.C. 103(a) as being unpatentable over Adams et al. US 6,306,840 for reasons of record. To repeat:

Adams et al. teaches structurally similar diamide compounds for the use as cell adhesion inhibitors. See formula I on col. 6 and note the definition of R_1, R_2, R_3, R_4, X and Y. Note these" R" groups corresponds to instant R_{11}, R_{10}, R_9, R_{12}, and R_8. Particularly note the R_2 meets the requirement of instant R_{10}. See Table 1 on col. 9 through col. 20 for compounds made.

Instant claims differ from Adams et al in requiring (un)substituted aryl for R_{10} whereas Adams et al. exemplifies only hydrogen and methyl groups for corresponding R_2.

However Adam et al. teaches the equivalency of exemplified substituents shown in Table I with that claimed for compound of formula I. See col. 6, formula I, especially the definitions of Y, R_1, R_2, R_3, and R_4. Thus it would have been obvious to one having ordinary skill in the art at the time of the invention was made to make compounds variously substituted ion the nitrogen and the side chain as permitted by the reference and expect resulting compounds (instant compounds) to possess the uses taught by the art in view of the equivalency teaching outline above.

Applicants' argument to overcome this rejection is not persuasive. The following apply

1. There is adequate guidance in Adams et al, to make the said compounds and expectation that these compounds would have the utility recited therein in view of equivalency of exemplified compounds with those claimed therein.

2. Although, applicants have provided testing prior art compounds, the comparison is deemed as not proper as it does not show such comparison. One is asked to guess what compound is compared and whether it is done under identical conditions and whether the evidence relied on commensurate with the scope of the instant claims. Note Ex parte Gelles 22 USPQ 2nd 1318, especially the following quote: " The evidence relied upon also should be reasonably commensurate in scope with the subject matter

claimed and illustrate the claimed subject matter " as a class" relative to prior art subject matter."

Hence this rejection is maintained.

Allowable Subject Matter

Claims 30-32 are allowed. Claims 17-19, 24-25, and 28 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims. Said claims would be allowed since specific types of species embraced in these claims are not taught or suggested by the art of record or from a search in the relevant art area.

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication from the examiner should be addressed to Venkataraman Balasubramanian (Bala) whose telephone number is (703) 305-1674. The examiner can normally be reached on Monday through Thursday from 8.00 AM to 6.00 PM. The Supervisory Patent Examiner (SPE) of the art unit 1624 is Mukund Shah whose telephone number is (703) 308-4716.

The fax phone number for the organization where this application or proceeding is assigned (703) 308-4556.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-1235.

V. Balasubramanian
Venkataraman Balasubramanian

09/29/2003